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(54) **Title**: POLYMORPH OF 8-HYDROXY-5- [(1R)-1-HYDROXY-2- [[(1R) -2-(4-METHOXYPHENYL) -1-METHYLETHYL] AMINO] ETHYL] -2(1H)-QUINOLINONE MONOHYDROCHLORIDE

(57) **Abstract**: The present invention relates to a novel polymorphic crystal form of 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]- amino]ethyl]-2(1H)-quinolinone monohydrochloride. The invention also relates to processes for its preparation, pharmaceutical compositions thereof, and to its use as a medicament.

POLYMORPH OF 8-HYDROXY-5- [(1R) -1-HYDROXY- 2- [[(1R)-2-(4-METHOXYPHENYL)-1-METHYLETHYL] AMINO] ETHYL]-2 (1H) -QUINOLINONE MONOHYDROCHLORIDE

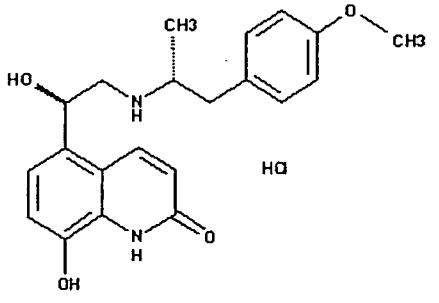
FIELD OF INVENTION

The present invention relates to a novel polymorphic crystal form of 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]-2(1H)-quinolinone monohydrochloride.

The invention also relates to processes for its preparation, pharmaceutical compositions thereof, and to its use as a medicament.

BACKGROUND OF THE INVENTION

8-Hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride (I) has been disclosed in EP 147719 as a bronchodilator having a potent beta-2-adrenoceptor stimulating action.



(I)

The compound, which has also been referred to in the literature with the codes TA 2005 and CHF 4226, may be prepared in a prevalently amorphous form in accordance with the method given in Example 4.

This compound, hereinafter referred to as CHF 4226, has been investigated for use as a medicament for treating inflammatory or obstructive airways diseases.

However, for preparing suitable pharmaceutical compositions, it is important that the compound is in a thermodynamically stable crystal form. It is also very important that the compound has good handling qualities and can be easily obtained on a commercial scale.

A thermodynamically stable crystal form of CHF 4226, hereinafter referred to as form A, has been disclosed and closely characterized in WO 2005/089760, but said form can be obtained in an adequate pharmaceutical level of chemical purity and crystallinity only by applying specific crystallization conditions.

Therefore, it would be advantageous to provide further thermodynamically stable crystal forms of CHF 4226, which are easy to obtain by crystallization, and characterized by a high level of chemical purity and crystallinity as well as good handling qualities for pharmaceutical use.

SUMMARY OF THE INVENTION

The invention relates to a novel polymorphic crystal form of 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride (CHF 4226), designated hereinafter as crystal form D.

Said polymorph is a thermodynamically stable anhydrous form, and is characterized by high level of chemical purity and crystallinity as well as good handling characteristics for the preparation of pharmaceutical compositions.

Crystal form D may be selectively produced by crystallization from appropriate solvents and conditions and is distinguishable based upon its characteristic peaks in the X-ray powder diffraction (XRPD) pattern, and its characteristic melting range.

Accordingly, the invention is also directed to processes for the preparation of said form, comprising crystallization or re-crystallization from appropriate solvents.

The invention is further directed to pharmaceutical compositions comprising CHF 4226 crystal form D herein described, and to its use as a medicament.

The polymorph of the invention is preferably administered by inhalation for the prevention and/or treatment of an inflammatory or obstructive respiratory disease such as asthma or chronic obstructive pulmonary disease (COPD).

Accordingly, in a further aspect, the present invention comprises the use of CHF 4226 crystal form D described before, for the prevention and/or treatment of an inflammatory or obstructive respiratory disease such as asthma or chronic obstructive pulmonary disease (COPD).

In a still further aspect, the present invention comprises a method of preventing and/or treating an inflammatory or obstructive respiratory disease such as asthma or chronic obstructive pulmonary disease (COPD), which comprises the inhalatory administration of an effective amount of CHF 4226 crystal form D described before.

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as it is commonly understood by one of skill in the art to which this subject matter belongs.

The term "amorphous" describes a non-ordered solid state characterized by a diffused X-ray powder diffraction with no sharp peaks.

The term "prevalently amorphous", describes a non-ordered solid state characterized by a diffused X-ray powder diffraction pattern with few sharp peaks.

"Polymorphism" is the ability of a compound to crystallize into more than one distinct crystal species. Polymorphs (or crystalline modifications) have an identical chemical structure but quite different physicochemical

properties.

An "effective amount" of a compound for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner reduce the symptoms associated with the disease.

"Thermodynamically stable" refers to a polymorphic form that, during storage under long-term conditions (25°C, 60% relative humidity), substantially does not convert into another one for a pharmaceutically acceptable period of time (at least 3 months, preferably 6 months, more preferably 1 year).

"High level of chemical purity" refers to a polymorph wherein the total amount of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC) or high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, is less than 5%, advantageously less than 2.5%, preferably less than 1.0, more preferably less than 0.5% w/w.

"High level of crystallinity" refers to a polymorph wherein the percentage of crystallinity is equal to or higher than 90%, preferably higher than 95% w/w as determined by standard methods of analysis used by those of skill in the art, such as X-ray powder diffraction or microcalorimetry.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is the differential scanning calorimetry (DSC) thermal trace of the crystal form D.

Figure 2 is the X-ray powder diffraction (XRPD) pattern of the crystal form D.

Figure 3 is the comparative DSC thermal trace of the crystal form A.

Figure 4 is the comparative XRPD pattern of the crystal form A.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel thermodynamically stable

crystal form of CHF 4226 having a high level of chemical purity and crystallinity, designated crystal form D.

Crystal form D is an anhydrous crystalline powder which can be characterized in a variety of ways.

Its thermal trace, shown in Figure 1, exhibits a melting peak at 170.7°C.

Crystal form D has the characteristic diffraction lines in the XPRD pattern thereof shown in Figure 2 using Cu-Kα radiation.

Said characteristic diffraction lines are reported in Table 1.

Table 1

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3,3873	2707,68	0,1506	26,08407	100,00
6,5379	196,48	0,2007	13,51986	7,26
8,3164	139,44	0,2342	10,63210	5,15
10,4880	66,40	0,2676	8,43501	2,45
12,1570	67,77	0,2007	7,28048	2,50
12,8490	313,23	0,2007	6,88991	11,57
13,4176	767,41	0,1840	6,59916	28,34
14,7949	63,27	0,4684	5,98777	2,34
16,4369	279,66	0,1673	5,39314	10,33
17,5646	63,31	0,3346	5,04934	2,34
18,6855	366,75	0,2676	4,74890	13,54
21,0160	401,78	0,4684	4,22726	14,84
21,4718	350,19	0,2676	4,13855	12,93
23,3344	260,20	0,2676	3,81224	9,61
24,8162	209,90	0,4684	3,58787	7,75
26,7332	90,83	0,4015	3,33478	3,35
28,4251	74,92	0,4015	3,14003	2,77
29,8453	124,85	0,4684	2,99376	4,61
33,8028	36,53	0,6691	2,65177	1,35
37,7254	34,89	0,5353	2,38458	1,29

Crystal form D shows stable features under several conditions of relative humidity. A demonstration is offered in Example 2.

The present invention also provides a process for the preparation of said

polymorph which comprises crystallizing raw CHF 4226 from a solution thereof in a solvent or a mixture of solvents under conditions which yield said crystal form.

The precise conditions under which said form is obtained may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

In general the polymorphic form of the invention may be prepared by crystallization under particular conditions of raw CHF 4226 obtained as reported in EP 147719 or by re-crystallization of the previously isolated crystal form A or by re-crystallization of any other crystal forms which may become known in the future.

Thus, for example, crystal form D may be prepared by crystallization from a solvent kept at the refluxing temperature (55-80°C).

In general, a solvent in which the solubility of CHF 4226 is low, e.g. acetone, acetonitrile or tetrahydrofuran, is used. In order to dissolve the starting material, it may be helpful to add an amount of water or methanol up to 15% v/v in the solvent system. The solution is then cooled to a temperature of 0-5°C at a cooling rate comprised between 5° and 10°C/hour, preferably 10°C/hour in order to bring form D crystals out from the solution.

The polymorph of the invention is readily isolable and it exhibits favorable filtration characteristics.

Optionally, it may be filtered off from the crystallization medium, after washing and drying.

The crystal form of the invention can be desiccated under gentle temperature conditions, and after drying it shows a low amount of residual solvents, typically less than 0.5% by weight.

If desired, crystal form D prepared as above may further be re-crystallized using crystallization conditions similar to those described

above.

For subsequent crystallizations, it may be preferable to add "seeds" of the crystalline material to the solution in order to induce crystallization.

The polymorph of the invention may be formulated for administration in any convenient way and the invention also refers to pharmaceutical compositions comprising CHF 4226 crystal form D.

The skilled person can establish without undue experimentation the effective dosage and/or the concentration of the active ingredient in the composition for a specific therapeutic purpose.

In the compositions provided herein, an effective concentration of the polymorph of the invention is mixed with one or more suitable pharmaceutical carriers or vehicles or excipients, for example those described in Remington's Pharmaceutical Sciences Handbook, Mack. Pub., N.Y., USA.

The concentration of the polymorph in the formulation is effective for delivery, upon administration, an amount sufficient to exert a therapeutically useful effect.

The compositions may also contain, if required, one or more other therapeutic agents, preferably those currently used in the treatment of respiratory disorders, e.g. corticosteroids such as budesonide and its epimers, beclometasone dipropionate, triamcinolone acetonide, fluticasone propionate, flunisolide, mometasone furoate, rofleponide and ciclesonide, anticholinergic or antimuscarinic agents such as ipratropium bromide, oxytropium bromide, tiotropium bromide, glycopyrrolate bromide, and the group of phosphodiesterase-4 (PDE-4) inhibitors such as roflumilast.

The polymorph of the invention may be formulated for oral, buccal, topical, parenteral, vaginal, rectal, or inhalation administration.

Inhalation administration is particularly preferred.

Upon said route of administration, the dose regimen is twice or once

daily, where the suitable dose is advantageously in the range of 0.5 to 8 μg, preferably of 1 to 4 μg, more preferably of 2 to 4 μg.

Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable solution or suspension formulations.

Advantageously, the inhalable powder formulations for inhalation comprise the polymorph of the invention in the form of interactive ordered mixtures.

More advantageously said formulations comprise a fraction of coarse particles of a physiologically acceptable excipient such as alpha-lactose monohydrate, said particles having a mass median diameter (MMD) higher than 90 micron, preferably the mass diameter (MD) comprised between 50 micron and 500 micron, more preferably between 150 and 400 micron, even more preferably between 210 and 355 micron.

Preferably said powder formulations further comprise a fraction of microparticles obtained by co-milling having a MMD lower than 35 micron, and constituted of particles of a physiologically acceptable excipient and an additive material selected from the class of the anti-adherents such as the amino acids leucine and isoleucine or of the lubricants such as magnesium stearate; sodium stearyl fumarate stearyl alcohol, stearic acid and sucrose monopalmitate.

More preferably said powder formulations comprise a fraction of microparticles having a MMD lower than 15 micron, preferably lower than 10 micron, constituted of particles of alpha-lactose monohydrate and particles of magnesium stearate.

Even more preferably, the inhalable powder formulations comprising the polymorph of the invention are prepared according to the teaching of co-pending application PCT/IB2007/0038924.

In general, CHF 4226 crystal form D may be used in preparation of a medicament for any disease or condition in which it is found therapeutically effective.

In view of its $beta_2$-adrenoceptor stimulating activity, CHF 4226 crystal form D is useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the *in vivo* guinea pigs model (see Kikkawa et al Biol Pharm Bull 1994, 17(8), 1047-1052) and analogous models.

Administration of the polymorph of the invention may be indicated for the prevention and/or treatment of mild, moderate or severe acute or chronic symptoms or for the prophylactic treatment of obstructive respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Other respiratory disorders characterized by obstruction of the peripheral airways as a result of inflammation and presence of mucus such as chronic obstructive bronchiolitis and chronic bronchitis may also benefit from its use.

The invention is further illustrated by the following examples.

Example 1 relates to the preparation of crystal form D, example 2 deals with stability experiments, example 3 refers to an exemplary formulation, and example 4 refers to the comparative characteristics of crystal form A.

EXAMPLES

Example 1 - Preparation of CHF 4226 crystal form D by crystallization

Crystallization is performed in a 500 ml jacketed glass reactor connected to thermocryostat, so that temperature can be accurately controlled; besides, crystallization is followed using a Lasentec FBRM D600 probe, so that nucleation and crystals growth could be monitored.

30 g of raw CHF4226 obtained as reported in EP 147719 is suspended in 250 ml of acetonitrile at refluxing temperature (55°C), and then 36 ml of

water (87:13 v/v) is added portionwise until dissolution is complete.

The solution is cooled to a temperature of 0-5°C at a cooling rate of 10°C/min.

After 20 hours, a solid sample is collected, filtered dried at T=40°C under vacuum, and analyzed for solid state, e.g. by XRPD and DSC.

Methods of analysis

1. X-ray powder diffraction (XRPD)

The XRPD analyses are carried out on a PANanalytical X'pert Pro X-ray powder diffractometer using Cu-Kα radiation. The instrument is equipped with a X'Celerator detector.

A theta-two theta continuous scan from 2.5 degrees 2 theta to 40 degrees 2 theta is used. Each sample is prepared for analysis by placing it in a quartz sample holder.

The XPRD patterns are reported in terms of degrees 2 theta (°2θ, accuracy ± 0.1°), diffraction peak intensity (height, [cts]), full width at half maximum (FWHM, [°2Th]), interatomic spacing in angstroms (d-spacing, [Å]), and relative intensities (%). The relative intensity is recorded as the ratio of the peak intensity to that of the most intense peak.

2. Differential scanning calorimetry (DSC)

The differential scanning calorimetry data are obtained on a Diamon Perkin Elmer Instrument.

The calibration standard used is indium. Approximately 2 to 5 mg of a sample is placed into a DSC pan and the weight is accurately measured and recorded. The pan is hermetically sealed. The sample is heated under nitrogen at a rate of 10°C/min, from 25°C to a final temperature of 200°C.

The results of the DSC and XRPD analysis are shown in Figures 1 and 2.

Yield: 12.4 g (41.3%).

Purity (HPLC): > 99%.

Example 2 - Stability studies

In order to check its thermodynamic stability, CHF 4226 crystal form D is stored at room temperature under different relative humidity (RH) conditions:

- 40% RH. and 25°C for 1 week
- 60% RH. and 25°C for 1 week
- 80% RH and 25°C for 1 week
- 60% RH and 25°C for 1 week
- 40% RH and 25°C for 1 week
- 30% RH and 25°C for 1 week
- 0% RH. and 25°C for 1 week
- 40% RH and 25°C for 1 week

The thermodynamic stability of all the samples is checked by recording their XPRD pattern.

Crystal form D show stable features under all stability screening conditions.

Example 3 - Exemplary inhalable dry powder formulation comprising CHF 4226 crystal form D.

The composition is reported in Table 2.

Table 2

Components	*Amounts*		
	Per shot of the inhaler		Single dose
	mg	%	µg
CHF 4226 crystal form D	0.004	0.04	4
alpha-lactose monohydrate 212-355 µm	8.996	89.96	
microparticles of alpha-lactose monohydrate and magnesium stearate obtained by co-milling	1.00	10.0	
Total weight	10		

Comparative Example 4

CHF 4226 crystal form A is prepared according to the Example of pending application WO 2005/089760.

Its thermal trace, shown in Figure 3, exhibits a melting peak at 190.0°C.

Crystal form A has the characteristic diffraction lines in the XPRD pattern thereof shown in Figure 4.

Said characteristic diffraction lines are reported in Table 3.

Table 3

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3,2171	4882,25	0,1673	27,46407	100,00
6,1648	56,30	0,2007	14,33719	1,15
11,0017	48,41	0,5353	8,04228	0,99
12,2932	221,92	0,2007	7,20012	4,55
13,6848	1628,41	0,2007	6,47093	33,35
14,9235	119,56	0,2007	5,93650	2,45
16,4033	1404,06	0,2007	5,40410	28,76
17,0392	72,21	0,2676	5,20383	1,48
18,0629	735,52	0,1673	4,91115	15,07
18,3442	579,41	0,1673	4,83647	11,87
19,4085	652,26	0,0836	4,57360	13,36
20,0887	115,52	0,2007	4,42025	2,37
22,0423	1972,56	0,2175	4,03270	40,40
22,9299	403,55	0,1171	3,87856	8,27
23,6648	552,77	0,2007	3,75976	11,32
24,3181	1607,95	0,2175	3,66022	32,93
25,0090	237,34	0,1673	3,56064	4,86
26,6661	452,07	0,3346	3,34302	9,26
28,6123	224,79	0,4015	3,11990	4,60
29,5322	204,45	0,2342	3,02478	4,19
30,6166	147,68	0,2676	2,92007	3,02
32,2879	129,66	0,2007	2,77264	2,66
33,9670	131,82	0,2676	2,63932	2,70
35,8516	103,81	0,2676	2,50479	2,13
38,2891	50,71	0,6691	2,35076	1,04

The results indicate that crystal form D is clearly distinguishable from crystal form A of CHF 4226.

Comparative Example 5

CHF 4226 is also prepared according to the Example 4 of EP 147719.

The compound is obtained in a prevalently amorphous.

However the diffraction lines in the XPRD pattern, reported in Table 4, allow establishing the obtained form is different and clearly distinguishable from crystal form D.

Table 4

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
3,2301	6070,87	0,1171	27,35334	100,00
6,2308	45,98	0,4015	14,18532	0,76
9,2012	39,49	0,4015	9,61152	0,65
12,3369	153,61	0,2007	7,17472	2,53
13,6352	1192,46	0,1171	6,49434	19,64
16,1071	311,73	0,2007	5,50282	5,13
16,8444	240,05	0,1338	5,26359	3,95
18,0251	426,10	0,2676	4,92137	7,02
18,7917	650,30	0,2007	4,72230	10,71
20,4675	57,55	0,4015	4,33929	0,95
21,4611	663,40	0,2007	4,14057	10,93
21,8671	918,91	0,1171	4,06462	15,14
22,8287	170,10	0,2676	3,89553	2,80
23,4886	410,61	0,2342	3,78756	6,76
24,6559	364,08	0,5353	3,61082	6,00
26,4968	90,38	0,5353	3,36400	1,49
28,3431	278,73	0,1338	3,14892	4,59
30,1299	111,82	0,4015	2,96613	1,84
32,2904	57,48	0,5353	2,77243	0,95
33,9931	76,27	0,2676	2,63736	1,26

CLAIMS

1. Crystalline 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride (CHF 4226) having the following characteristic XRPD peaks at 2θ in angular degrees using Cu-Kα radiation (accuracy ± 0.1°): 3.39, 6.54, 8.32, 10.49, 12.16, 12.85, 13.42, 14.79, 16.44, 17.56, 18.69, 21.02, 21.47, 23.33, 24.82, 26.73, 28.43, 29.85, 33.80, and 37.73.

2. A process for preparing the crystal form of claim 1 which comprises the step of crystallizing raw 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride from a solution thereof in a solvent selected from the group consisting of acetone, acetonitrile and tetrahydrofuran, kept under a refluxing temperature.

3. The process as claimed in claim 2 wherein the solution is cooled down to a temperature of 0-5°C at a cooling rate comprised between 5 and 10°C/min.

4. A pharmaceutical composition comprising the crystal form of claim 1 in admixture with a pharmaceutically acceptable carrier.

5. The pharmaceutical composition as claimed in claim 4 further comprising a therapeutic agent selected from the group consisting of corticosteroids, anticholinergic or antimuscarinic agents and phosphodiesterase-4 (PDE-4) inhibitors.

6. The pharmaceutical composition as claimed in claim 4 or 5 in the form of an inhalable aerosol comprising a propellant.

7. The pharmaceutical composition as claimed in claim 4 or 5 in the form of an inhalable powder.

8. Use of the crystal form of claim 1, as a medicament.

9. Use of the crystal form D of claim 1 for the prevention and/or treatment of an inflammatory or obstructive respiratory disease.

10. Use of the crystal form of claim 1, in the manufacture of a medicament for the prevention and/or treatment of an inflammatory or obstructive respiratory disease.

11. The use according to claim 9 or 10, wherein the respiratory disease is asthma or chronic obstructive pulmonary disease (COPD).

Figure 1

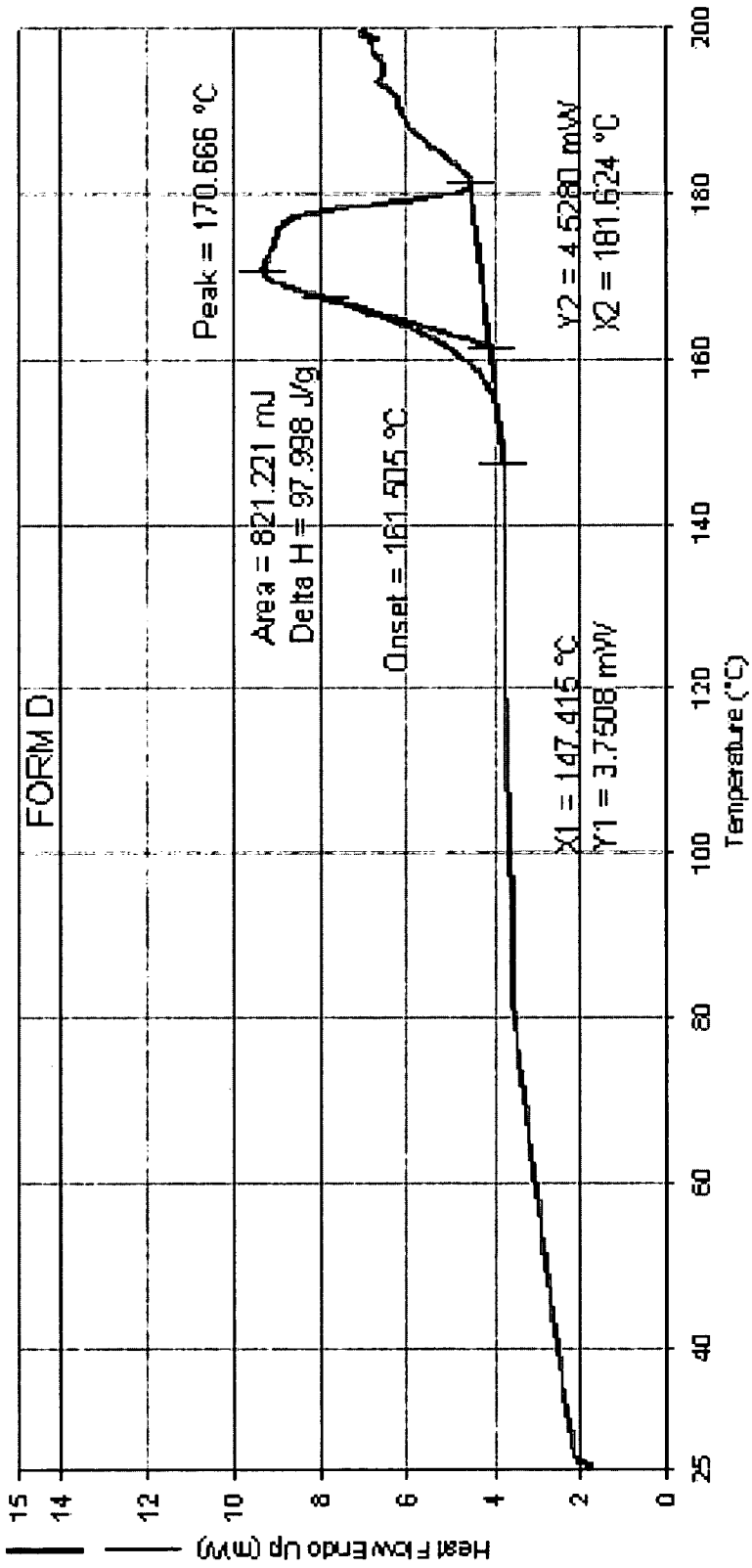

FORM D
Peak = 170.666 °C
Area = 821.221 mJ
Delta H = 97.998 J/g
Onset = 161.505 °C
X1 = 147.415 °C
Y1 = 3.7508 mW
Y2 = 4.5280 mW
X2 = 181.624 °C
Heat Flow Endo Up (mW)
Temperature (°C)
15
14
12
10
8
6
4
2
0
25
40
60
80
100
120
140
160
180
200

Figure 2

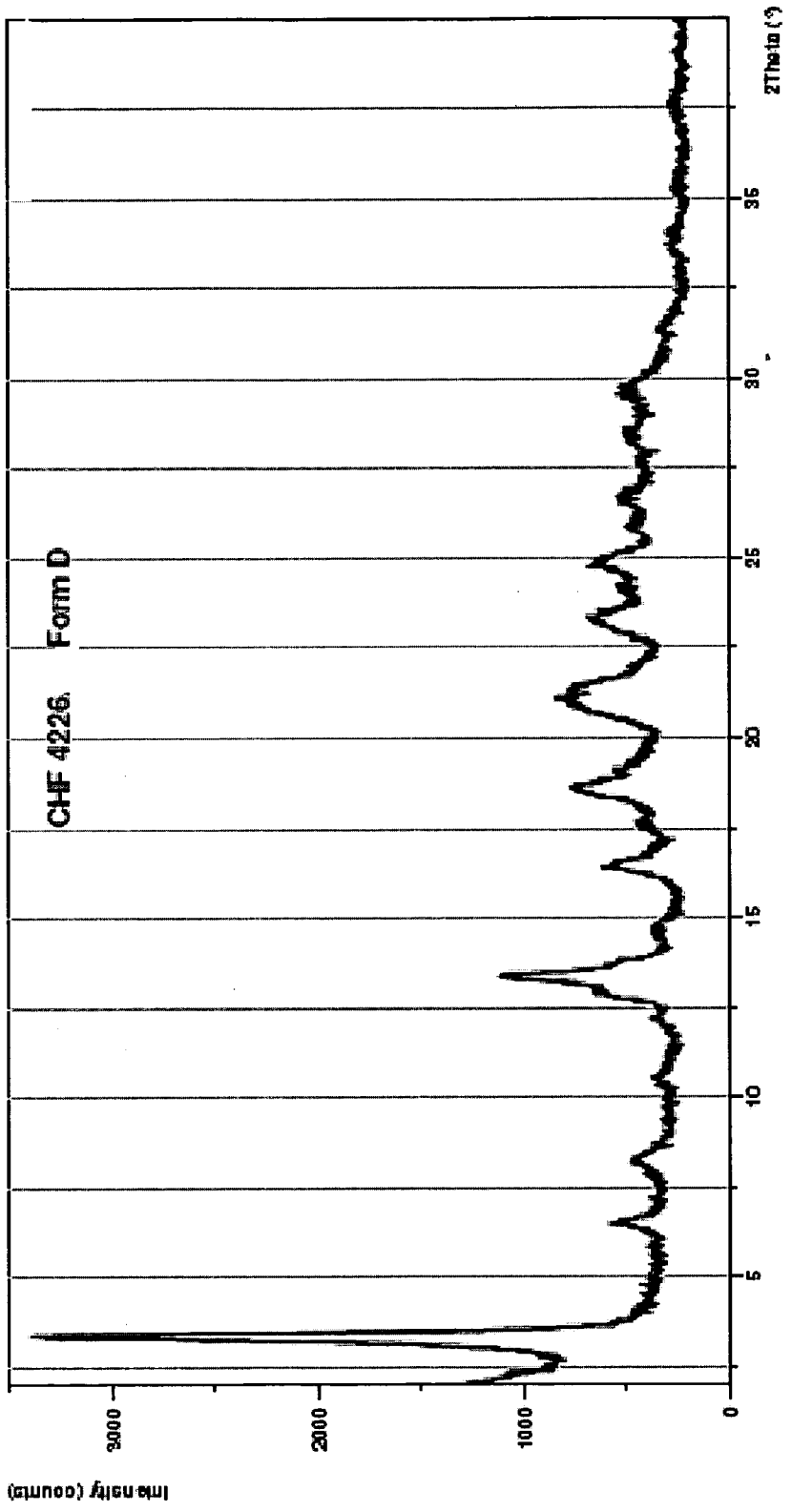

CHF 4226 Form D
Intensity (counts)
2Theta (°)
0
1000
2000
3000
5
10
15
20
25
30
35

Figure 3

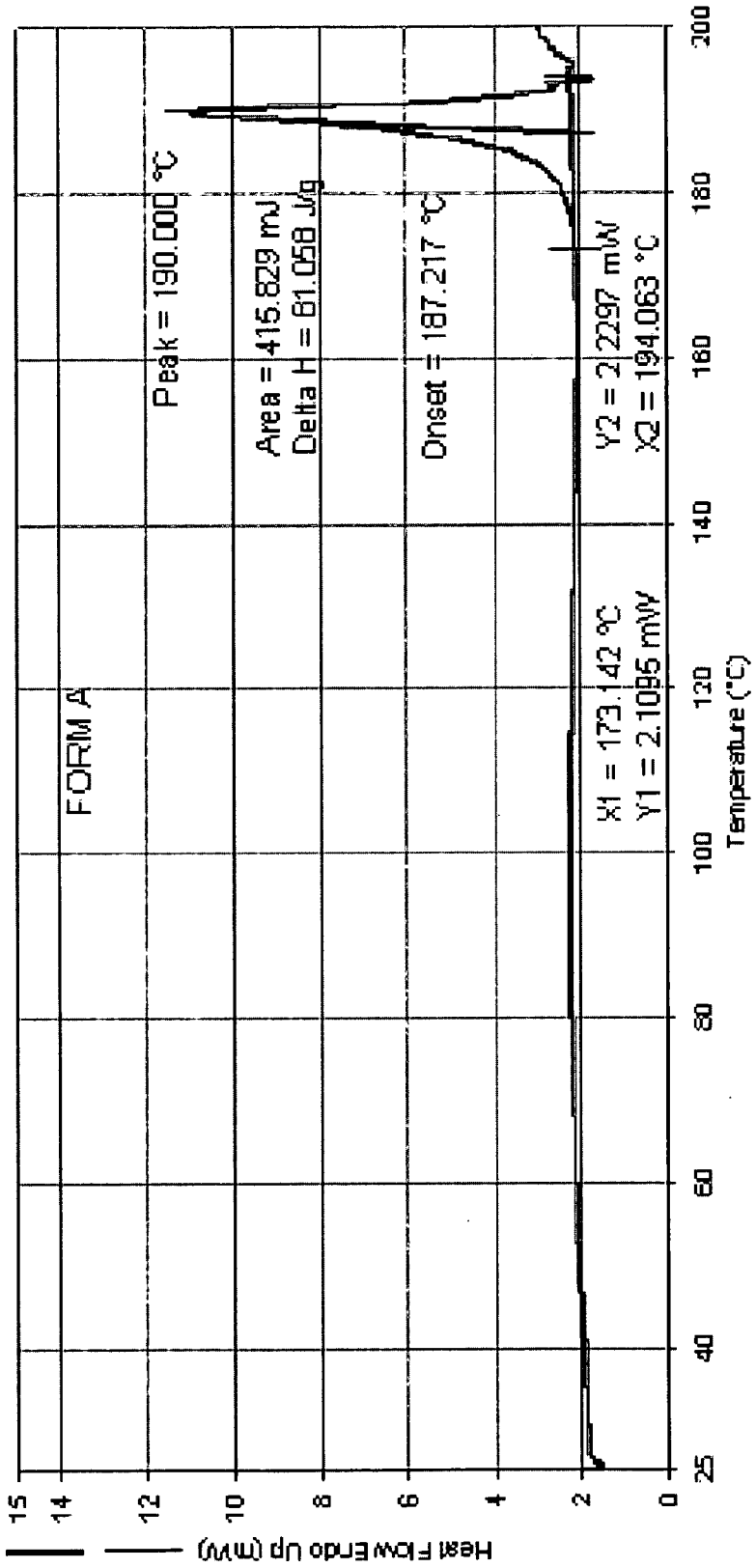
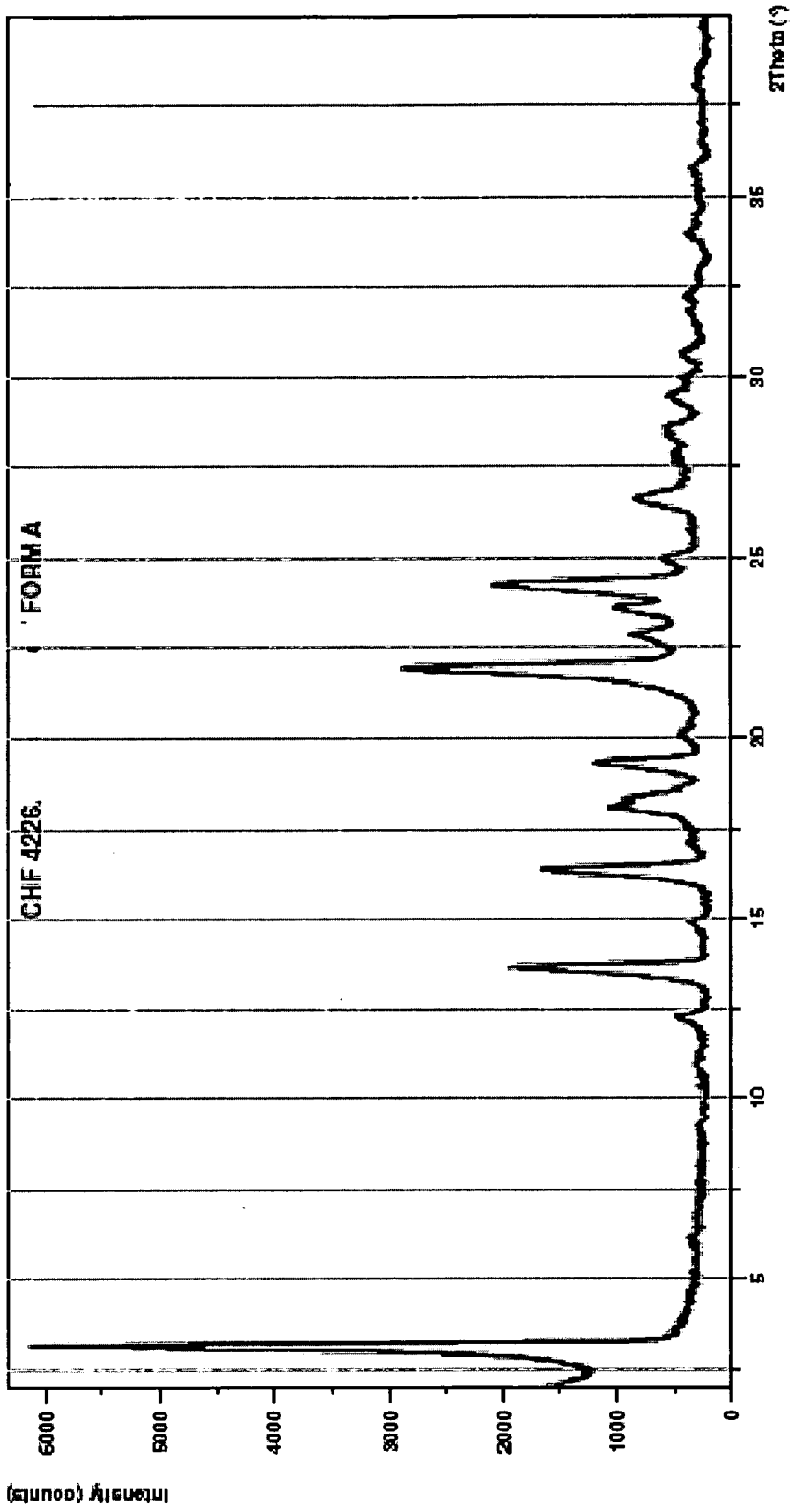

FORM A
Peak = 190.000 °C
Area = 415.829 mJ
Delta H = 81.058 J/g
Onset = 187.217 °C
X1 = 173.142 °C
Y1 = 2.1095 mW
Y2 = 2.2297 mW
X2 = 194.063 °C
Heat Flow Endo Up (mW)
Temperature (°C)
15
14
12
10
8
6
4
2
0
25
40
60
80
100
120
140
160
180
200

Figure 4


FORM A
CHF 4226.
Intensity (counts)
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
2Theta (°)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/002549

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/26 A61K31/4704 A61P29/00 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2005/089760 A (CHIESI FARMA SPA [IT]; PIVETTI FAUSTO [IT]; PIGHI ROBERTO [IT]) 29 September 2005 (2005-09-29) cited in the application the whole document In particular pages 8-10 -----	1-11
P,X	EP 1 953 143 A (CHIESI FARMA SPA [IT]) 6 August 2008 (2008-08-06) abstract; claims 1-14; example 3 -----	1-11

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2009	21/07/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofia

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/002549

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

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International application No
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